REMARKS

The Office Action of July 28, 2004 presents the examination of claims 1-6, 8-26, 34-45, 47, 51 and 52, claims 27-33 and 48-50 being withdrawn from consideration following a Restriction Requirement.

All of claims 1-52 are canceled herein, being replaced by new claims 53-85. The new claims are directed to similar subject matter as the prior claims, i.e. chimeric PIV comprising a background PIV genome or antigenome and one or more heterologous genes or genome segments, and corresponding immunogenic compositions, expression vectors and methods for making the chimeric viruses. Some of the present claims include features of the heterologous genes or genome segments that are different from those considered to this point in prosecution, i.e. the site of insertion or the specific nature of the heterologous gene or genome segment.

Support for the new claims

New claims 53 and 69 recite that the chimeric PIV comprises one or more genes or genome segments encoding an HN and/or F glycoprotein gene or an antigenic determinant thereof from HPIV1 or HPIV2 inserted into an HPIV3 "background" genome or antigenome. The chimeric virus includes a wild-type L protein gene of the background PIV and the resulting chimeric virus is attenuated at least 10-fold in the respiratory tract of a primate host infected with the chimeric virus.

The inclusion of HN and/or F genes or antigenic determinants thereof in a HPIV3 background is the subject matter of original claim 4. The inclusion of a wild-type L protein is supported by the specification at, e.g. page 13, lines 8-10 (the virus includes an L protein) taken with working examples that use wild-type L protein and are distinct from examples using cp45 L protein (e.g. as disclosed at page 17, lines 10-12).

Attenuation of at least 10-fold *in vivo* in the respiratory tract of a primate host is described in the specification at, e.g. page 70, lines 6-10 and page 71, lines 20.

New claims 54 and 70 recite that the heterologous gene or genome segment is inserted at a site selected from the group consisting of a site between the P and M open reading frames, a

site between the N and P open reading frames, a site between the HN and L open reading frames. This feature of the invention is described in the specification at, e.g. Figures 3 and 6, Example 1 beginning at page 79 and Example 6 beginning at page 103.

New claims 58-59, 63, 74-75 and 79 describe insertion of a genome segment including a gene start and gene end sequence or insertion into a non-coding region of the HN gene. These embodiments of the invention are described at, e.g. Figure 6 and page 78, lines 22-32

New claims 60 and 76 recite insertion of a genome segment that does not encode a protein. This embodiment of the invention is disclosed at, e.g. page 78, line 28 to page 79, line 2.

New claims 61, 62, 77 and 78 recite that the inserted genome segment has a length of at least 995 nucleotides. This is described in the specification at, e.g. Table 10 at page 108.

Claims 65 and 81 recite that the inserted genome segment has a length of at least 3000 nucleotides. This is described in the specification at, e.g. page 78, line 26.

Claims 66 and 82 describe that the heterologous gene or genome segment is obtained from measles virus. This is described, e.g. in Figure 1A and 1B.

Claims 67 and 83 represent the subject matter of original claim 20.

New claim 68 recites an immunogenic composition. Such is described in great detail beginning at page 68, line 7. An "immunologically effective amount" of the virus is described at page 69, lines 6-8.

New claim 84 recites an expression vector comprising a promoter, a polynucleotide encoding a complete or partial chimeric viral genome or antigenome, and a transcription terminator sequence. These elements of the expression vector are described at, e.g. page 58, lines 3-25.

New claim 85 describes a method for making the chimeric virus by expression of a chimeric viral genome or antigenome together with N, P and L proteins of PIV, wherein any one or all of the N, P and L proteins can be encoded either by the chimeric virus genome or antigenome, or by one or more separate expression vectors. Such is described at, e.g. page 58, line 26 to page 61, line 2.

Substance of the Interview

A personal interview with the Examiner and her Supervisor was held on July 13, 2005 and a further telephone discussion with the Examiner was held later that day. Applicants wish to thank the Examiner and her Supervisor very much for providing so much of their time to help resolve the issues in this matter.

Applicants first addressed the Collins and Klein references of record. Applicants explained that Collins (US 6,264,957) is not citable to support an obviousness rejection, being prior art only under 35 USC section 102(e) and subject to common ownership with the present application at the time the invention was made. Klein was explained as irrelevant to the present invention, being directed to producing subunit vaccines that are composed of proteins expressed in *in vitro* cultures.

Applicants presented proposed claim amendments that were considered by the Examiner and further explained how the amended claims were patentable over the Belshe reference (US 5,869,036). The Examiner or her supervisor provided some comment upon the proposed claims, such comments generally being limited to suggestions for avoiding possible rejections for lack of written description. It was acknowledged that Applicants' proposed claims, which are reflected in the claims presented in this paper and include the suggestions of the Examiner or her Supervisor, would likely be considered to distinguish the invention over Belshe.

The Examiner also agreed that claims to embodiments of chimeric viruses, immunogenic compositions comprising such viruses, isolated polynucleotides constituting the genomes of such viruses, expression vectors constituting such polynucleotides, methods for making the chimeric viruses, and methods for immunization using the viruses, would all be examined in the present application if presented.

Issues raised in the Office Action

Claims 1, 3-6, 8-18, 21, 22, 24, 25, 34, 37-39, 41-43, 51 and 52 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. Claims 1-6, 8-26, 34-45, 47, 51 and 52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). Claims 1-6, 8-26, 34-35, 47, 51

and 52 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 10 and 11 of the copending application 09/733,692.

Rejection for obviousness-type double patenting

Applicants note the provisional nature of the standing rejection for obviousness-type double patenting. Applicants submit that this rejection should be held in abeyance until at least one of the co-pending applications is allowed. Applicants note that the claims in the entire group of five co-pending applications related to chimeric PIV inventions have been completely re-written and in this process, Applicants' Representative attempted to minimize overlap of the claims among the various applications. It is acknowledged that some overlap among the applications may be found. Applicants will address any obviousness-type double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Rejection for anticipation

Claims 1, 3-6, 8-18, 21, 22, 24, 25, 34, 37-39, 41-43, 51 and 52 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. The rejected claims are all canceled, rendering this rejection moot. Applicants submit that the instant rejection should not be applied to the present claims.

Applicants have previously argued that Belshe '036 is not enabling of its disclosed embodiments and Applicants maintain their view that such is the case. However, the USPTO has made clear, in this and other applications of the Applicants, their position that concession that Belshe is not enabling of its disclosure includes an admission that the reference does not enable its claims and would therefore be invalid and that such a finding will not be made without intercession of the Board of Appeals or other higher authority than the Examining Corps.

Accordingly, Applicants provide here an explanation of the differences between the presently-claimed invention and what is disclosed by Belshe '036.

The entirety of the Belshe '036 patent relies upon extrapolation from a single kind of experiment. That is, all of Belshe's speculation comes from the result of experiments in which

growth of a cp45 strain of HPIV3 at various temperatures is complemented by a plasmid expressing one or more of the NP, P and L protein of the wild-type HPIV3. This experiment is summarized in the attached Exhibit 1.

HPIV3 strain cp45 was known to exhibit a temperature sensitive phenotype for replication, such that, at 39.5 °C, the replication of the virus is nil (see Table 1 at col. 6). Complementation by a plasmid expressing wild-type HPIV3 L protein provides some very small degree of recovery of virus plaques at the non-permissive temperature; about 300 or so plaques were formed, in comparison with the yield of 8×10^6 seen for the wild-type HPIV3 (compare Table 3 at col. 8 with Table 1 at col. 6).

Belshe concluded that the temperature sensitive replication phenotype of the cp45 virus was due to mutations in the L protein. From this single conclusion, Belshe et al. speculate about how a recombinant virus can be constructed.

Applicants have previously argued strenuously that Belshe does not establish any kind of expectation of success in making the "hybrid" viruses that he describes or in making the present invention. However, as to the present claims, the Examiner should consider a few things about the Belshe reference.

First, the only genome described by Belshe et al. is a non-recombinant genome of the cp45 strain. Belshe et al. do not describe any sort of recombinant genome; they mention at col. 9, lines 64-66 that Example 7 "details methods for producing attenuated hybrid vaccines for target viruses...". However, Example 7 only provides citations of papers that describe the nucleic acid sequences of various viral genes. Belshe does state at the bottom of col. 8 that, "The gene sequence which encodes the surface glycoproteins of a target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a hybrid virus." However, there is no further description of how this might be accomplished. At col. 9, lines 6-19, Belshe et al. describe that a hybrid virus should contain the 3' leader of cp45, NP, P[+C] and M proteins of cp45, a sequence encoding at least one surface glycoprotein of "an enveloped target virus" and "a variant protein which is different from the L protein of wild-type HPIV 3." All of the remaining disclosure of Belshe emphasizes that the L protein of any hybrid virus must be a variant from the wild-type L protein of cp45.

At the bottom of col. 6, Belshe et al. state that changes in the neuraminidase protein provide only minor decreases in replication, by less than a factor of 10, and therefore this protein is not a major factor in the attenuation of cp45. Belshe et al. also note that perhaps changes in the 3' leader sequence are "suspected in affecting the cold adaptive, temperature sensitivity and/or attenuation phenotypes of cp45." Thus, the only significant mechanism of attenuation that Belshe discloses or suggests is mutation of the L protein to a temperature sensitive phenotype by one or more point mutations.

To summarize, Belshe et al. only describe use of a cp45 genome or antigenome, having at least two of three defined point mutations in the L protein, to obtain an attenuated HPIV3 virus. The cp45 genome is a genome of a HPIV strain. Mutation of the L protein, and perhaps (though not definitively) in the 3' leader sequence, is the only mechanism of attenuation disclosed or suggested. Belshe et al. suggest that such an attenuated HPIV3 virus might be modified by substitution of its genes encoding the HN and/or F glycoproteins with the corresponding entire genes from a "target virus" among those listed at col. 8, lines 42-58. However, as explained above, and in painstaking detail previously, Belshe et al. provide no disclosure whatsoever about how to accomplish such substitution.

On the other hand, the present claims 53 and 69 recite that at least 10-fold attenuation of replication of the virus is observed in the respiratory tract of a primate host, despite the inclusion of a wild-type L protein gene in the chimeric viral genome or antigenome. Such a result is directly contrary to the teachings of Belshe '036, which indicates that mutation of the L protein is necessary for attenuation of replication.

The present claims 54-66 and 70-82 recite that a heterologous gene or genome segment is inserted at a site between the P and M ORF, the N and P ORF or the HN and L ORF. This feature of the invention is not at all disclosed, expressly or inherently, by Belshe '036, as Belshe only contemplates at most substitution of the endogenous glycoprotein gene for a heterologous glycoprotein gene (and it is not conceded by Applicants that such is adequately described by Belshe '036). Furthermore, Belshe et al. do not at all teach that attenuation can be achieved by insertion of a heterologous gene or gene segment into a site between the P and M ORF, the N and P ORF or the HN and L ORF (see, e.g. claim 56).

Claims 58, 59 and 60, and the corresponding claims 74, 75 and 76 recite further features of the inserted genome segment that it comprises a gene start and gene end sequence of the background PIV genome or antigenome, or that it is inserted into the non-coding portion of the HN gene, or that it does not encode a protein. None of these features of the invention are at all contemplated by Belshe '036.

Claims 67 and the corresponding claim 83 recite that the L protein of the HPIV3 background genome or antigenome should be mutated at amino acid 456. This mutation is not at all contemplated by Belshe '036.

Each of claims 68, 84 and 85 depend from all of the above claims and so are novel over Belshe '036 for at least the above reasons.

Rejection for obviousness

Claims 1-6, 8-26, 34-45, 47, 51 and 52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). The rejected claims are all canceled, rendering this rejection moot. Applicants submit that the instant rejection should not be applied to the presently pending claims.

As explained in the interview, Collins '957 is not available to the Examiner to make a rejection grounded on 35 U.S.C. § 103(a). 35 U.S.C. § 103(c). The present application was filed after November 29, 1999 and Collins '957 was assigned to the same entity, the Government of the United States of America as represented by the Department of Health and Human Services, as the present application was to be assigned at the time the present invention was made. This is evidenced by the eventual assignment of this application to that entity recorded at reel 011182, frame 0053 on September 25, 2000. Applicants' Representative notes that all of the inventors named on this application were employees of the National Institutes of Health and had an obligation, via an employment agreement, to assign their rights in the present invention to the Government of the United States of America as represented by the Department of Health and Human Services at the time the invention was made. Applicants will present evidence of such employment agreements at the request of the Examiner.

As was also explained in the interview, Klein '207 is not at all relevant to the present invention. Klein et al. describe making chimeric antigens, for example a chimera of a glycoprotein of a PIV with a glycoprotein of RSV, and then expressing the chimeric protein as a heterologous protein from a eukaryotic host cell in culture. See, for example, Examples 5-7, beginning at page 18 of the reference, describing expression of F_{PIV3}-F_{RSV} chimeric glycoprotein F from a baculovirus vector in Sf9 cells.

Such disclosure is remote from the present invention, in which a genome for a live, infectious, chimeric parainfluenza virus is constructed. Though perhaps providing description of what might be an interesting gene for an antigen to include in a genome of a live, chimeric PIV, Klein '207 tells one of ordinary skill in the art nothing at all about any other feature of the present invention, nor anything about how to make or use the present invention.

As the Collins reference of the combination is not available to the Examiner, Applicants submit that the present invention is not *prima facie* obvious over Belshe '036 or Belshe '036 combined with Klein.

As explained above, Belshe '036 does not disclose or in any way suggest the following features of the invention:

1. that at least 10-fold attenuation of replication of the virus is observed in the respiratory tract of a primate host, despite the inclusion of a wild-type L protein gene in the chimeric viral genome or antigenome;

2. that a heterologous gene or genome segment is inserted at a site between the P and M ORF, the N and P ORF or the HN and L ORF;

3. that the inserted genome segment comprises a gene start and gene end sequence of the background PIV genome or antigenome;

4. that a gene or genome segment is inserted into the non-coding portion of the HN gene;

5. that an inserted genome segment does not encode a protein;

6. that the L protein of the HPIV3 background genome or antigenome should be mutated at amino acid 456.

Thus, the present invention is not obvious in view of Belshe '036 alone.

Klein '207 makes no disclosure that an infectious, chimeric PIV should incorporate a genome including any one or more of the features listed above. Accordingly, Klein '207 does not remedy the deficiency of Belshe '036 to establish *prima facie* obviousness of the presently-claimed invention and the present invention is not obvious over Belshe '036 in view of Klein '207.

For the above reasons, the rejection of 1-6, 8-26, 34-45, 47, 51 and 52 under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207) should not be applied to the present claims 53-85.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Dated: August 26, 2005

Respectfully submitted,

By _____

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